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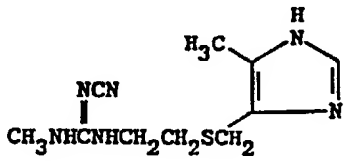
(54) Title: USE OF CIMETIDINE FOR WEIGHT LOSS



(57) Abstract

This invention relates to a new use of a histamine H_2-antagonist and in particular to the use of such a compound to achieve reductions in bodyweight, particularly with patients on a calorie-controlled diet.

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USE OF CIMETIDINE FOR WEIGHT LOSS

This invention relates to a new use of a histamine H_2-antagonist and in particular to the use of such a compound to achieve reductions in bodyweight, particularly with patients on a calorie-controlled diet.

Histamine H_2-antagonists are a class of drug which inhibit gastric secretion of acid and are useful in the treatment of duodenal and benign gastric ulceration, reflux oesophagitis and conditions where reduction of gastric secretion and acid output is desirable. The class of compounds includes cimetidine, ranitidine, famotidine, nizatidine, roxatidine and sufotidine.

U.S. Patent 4220653 (Vivino) was filed in January 1979 and published in September 1980. As the preferred embodiment this suggested that a 300mg. tablet of cimetidine taken at the completion of every meal tended to suppress the feeling of hunger which overweight persons sometimes experience, and assisted weight loss. U.S. Patent 4293562 (Ritter) filed July 2 1979 and published October 6 1981 described a combination of cimetidine with an anorexant amphetamine for use in facilitating weight loss. The preferred dose was 300 mg cimetidine and 5 mg dextroamphetamine sulphate, which was preferably taken in conjunction with breakfast. There do not appear to have been any subsequent publications which have supported or confirmed these suggestions.

Cimetidine was the first histamine H_2-antagonist marketed and since its launch in 1976 has been the subject of intensive post-marketing surveillance covering millions of patients. In all countries, with the recent exception of Denmark, cimetidine and all other histamine H_2-antagonists have only been available on prescription

from a medically-qualified practitioner for the treatment of gastrointestinal disorders.

There have not been any reports of significant loss or gain in bodyweight following standard treatment with cimetidine or any other histamine H_2-antagonist. In particular Walan A. and Ström M., Scand. J. Gastroenterol., 20 (Suppl. III) 24-30 (1985) reported that there was no change in the median bodyweight of 67 patients taking 400 or 800mg. cimetidine daily over a three-year period. In this study the timing of the dose was stated to be "400mg at bed-time or twice a day". The standard prescribing information for cimetidine has always indicated that the compound should be taken at mealtimes.

Surprisingly, it has now been discovered that if cimetidine is administered orally before meals to an overweight patient on a calorie-restricted diet there is a significant enhancement of the reduction in bodyweight.

Preferably the cimetidine is administered as a liquid suspension, particularly preferably as a viscous suspension and especially as a suspension having a viscosity of from about 2000 to about 5000 mPa.s (cps) at 25°C. Preferably a liquid suspension is flavoured with a low-calorie sweet flavour and an agent such as Contramarum which masks the bitter taste of the cimetidine. Preferably the flavour is peppermint, butterscotch or apricot.

Preferably if cimetidine is in the form of a liquid suspension it is administered from about 45 to about 10 minutes before each meal, particularly preferably about 30 minutes before each meal.

Preferably if the cimetidine is in tablet form it is administered from about 2 hours to 30 minutes before each meal, for example from 90 minutes to 45 minutes before meals, preferably about 1 hour before each meal.

Preferably the unit dose of the cimetidine taken before each meal will be about one-quarter the daily dosage for the treatment of a duodenal ulcer or about one-quarter the daily dosage for maintenance therapy. Preferably the unit dose will contain 150 to 300 mg. cimetidine, particularly 200mg.

In addition to taking the cimetidine before meals patients can also take a unit dose when they experience strong hunger sensations between meals provided that a total daily dose of 1000mg is not exceeded.

Preferably the cimetidine is administered as a liquid suspension, especially a suspension comprising 200mg cimetidine in from 2 to 20 ml. Particularly preferably the cimetidine is administered as a viscous suspension and especially as a suspension having a viscosity of from about 2000 to about 5000 mPa.s (cps) at 25°C (Brookfield Spindle LV4 at 60 rpm reading after 30 sec. rotation), such as the product 'Tagagel' (trademark of SmithKline Beecham plc and subsidiaries thereof). Most conveniently the suspension is packaged in the form of a sachet, each sachet containing 5 or 10 ml suspension.

Preferably subjects restrict their daily intake to between 1500 and 1200 Kcals, ideally about 1200 Kcals, taken only as three main meals. Preferably added fibre is included in the diet. Preferably the amount of added fibre will be from 3g to 30g daily, for example from 5 to 15g daily or 6 to 12g daily and especially about 9g daily.

Preferably the fibre is taken in the form of cooked or uncooked bran, fibrous grain extract or fibrous citrus extract, or mixtures thereof. Preferably the fibre is taken with meals, or immediately before meals. Alternatively the fibre can be taken with the cimetidine. Preferably the fibre is not eaten dry, but is pre-moistened or taken with liquids. A preferred type of fibre is that sole as "Fiberform" in Sweden by Tricum AB.

Preferably subjects take moderate exercise, such as walking moderately fast, for 15 to 60 minutes per day, especially about 30 minutes per day.

Preferably the cimetidine is taken daily for a period of 8 to 12 weeks, and thereafter subjects should control their food intake and exercise such that they stay at essentially the same weight for the following three months.

To establish the benefits of the invention a study was carried out on 60 patients (55 women, 5 men) aged 16-56 years who were overweight with excess bodyfat, bodyweight above body mass index (BMI) between 25 and 37 kg/m^2.

Over 8 weeks the patients received either 'Tagagel' suspension (10ml, 20mg/ml, i.e. 200mg. cimetidine) or a matching placebo three times a day 30 minutes before main meals and were put on a diet with an energy content of about 1200 Kcal/day with added dietary fibre ('Fiberform R' 9g. per day). 'Tagagel' is a registered trademark for a suspension of 200mg. cimetidine in 10mls. of a viscous buffered solution having a viscosity of about 3500 mPa.s which is sold in sachet form by SmithKline Dauelsberg GmbH. During the trial, the patients, on a weekly basis,

recorded the degree of hunger before each meal on a line with the endpoints "no hunger" (0) and "extremely hungry" (100).

The reduction in weight as percentage of the pre-trial weight was 9.5 ± 2.1kg. or 12.2 ± 2.9% in the cimetidine group and 2.8 ± 1.3kg. or 2.8 ± 1.5% (SD) in the placebo group (95% confidence limits), and the difference between the groups highly significant ($p < 0.001$) see Figure 1. The lowering of BMI was 3.33 ± 0.76kg/m^2 and 0.76 ± 0.42 in the cimetidine and the placebo group respectively ($p < 0.001$). In the active group there were significantly greater decreases in the circumference around the waist and the hip: 8.6 ± 3.9 and 7.8 ± 3.1cm respectively for the cimetidine group and 2.2 ± 1.5 and 2.1 ± 1.5cm for the placebo group (95% confidence limits). The difference between the two groups was highly significant ($p < 0.001$). See Figure 2.

The assessment of feeling of hunger on the visual analogue scale showed differences between the two groups with highly significant less hunger feelings being reported at all three meals in the cimetidine group compared to the placebo group. In Figure 3 the mean value of the three meals is demonstrated in the two groups.

Side effects were rare and almost equally distributed between the groups.

Claims:

1. The use of cimetidine in liquid form in the non-medical treatment of excess body weight, or for the control of bodyweight when food intake in calories is in excess of requirements.

2. The use of cimetidine for the manufacture of a liquid medicament for the therapeutic treatment of obesity.

3. A method of reducing the weight of a person suffering from excessive weight which comprises orally administering to said person an effective amount of cimetidine regularly before mealtimes in conjunction with a calorie-controlled diet.

4. A use according to Claim 1 or 2 in which the cimetidine is administered regularly before mealtimes.

5. A method according to Claim 3 in which cimetidine is taken as a liquid formulation.

6. A method according to Claims 3 or 5 in which the cimetidine is administered in the form of a viscous suspension.

7. A method according to Claim 6 in which the cimetidine is administered 30 minutes before meals.

8. A method according to any one of Claims 3 or 5 to 7 in which the unit dose is 200mg. cimetidine.

9. A method according to any one of Claims 3 or 5 to 8 in which the unit dose of cimetidine is in the form of a sachet.

10. A method according to any one of Claims 3 or 5 to 9 in which the cimetidine is coadministered with dietary fibre.

Table I

PRE-TRIAL DATA
Mean ± SD

	ACTIVE	PLACEBO
Age (years)	39 ± 12	40 ± 12
Duration of overweight (years)	9.2 ± 10.0	9.9 ± 13.1
Weight (kg)	78.9 ± 11.0	77.7 ± 14.4
Height (cm)	169 ± 6	162 ± 10
Waist measure (cm)	88 ± 11	87 ± 10
Hip measure (cm)	104 ± 8	109 ± 10
BMI (kg/m^2)	27.72 ± 3.27	27.62 ± 4.03
Syst BP (mm Hg)	142 ± 20	137 ± 17
Diast BP (mm Hg)	86 ± 10	84 ± 9
Alcohol consump. (yes/no)	6/24	10/20
Smoking (yes/no)	8/22	11/19
Physical activity (yes/no)	10/20	11/19

Figure I

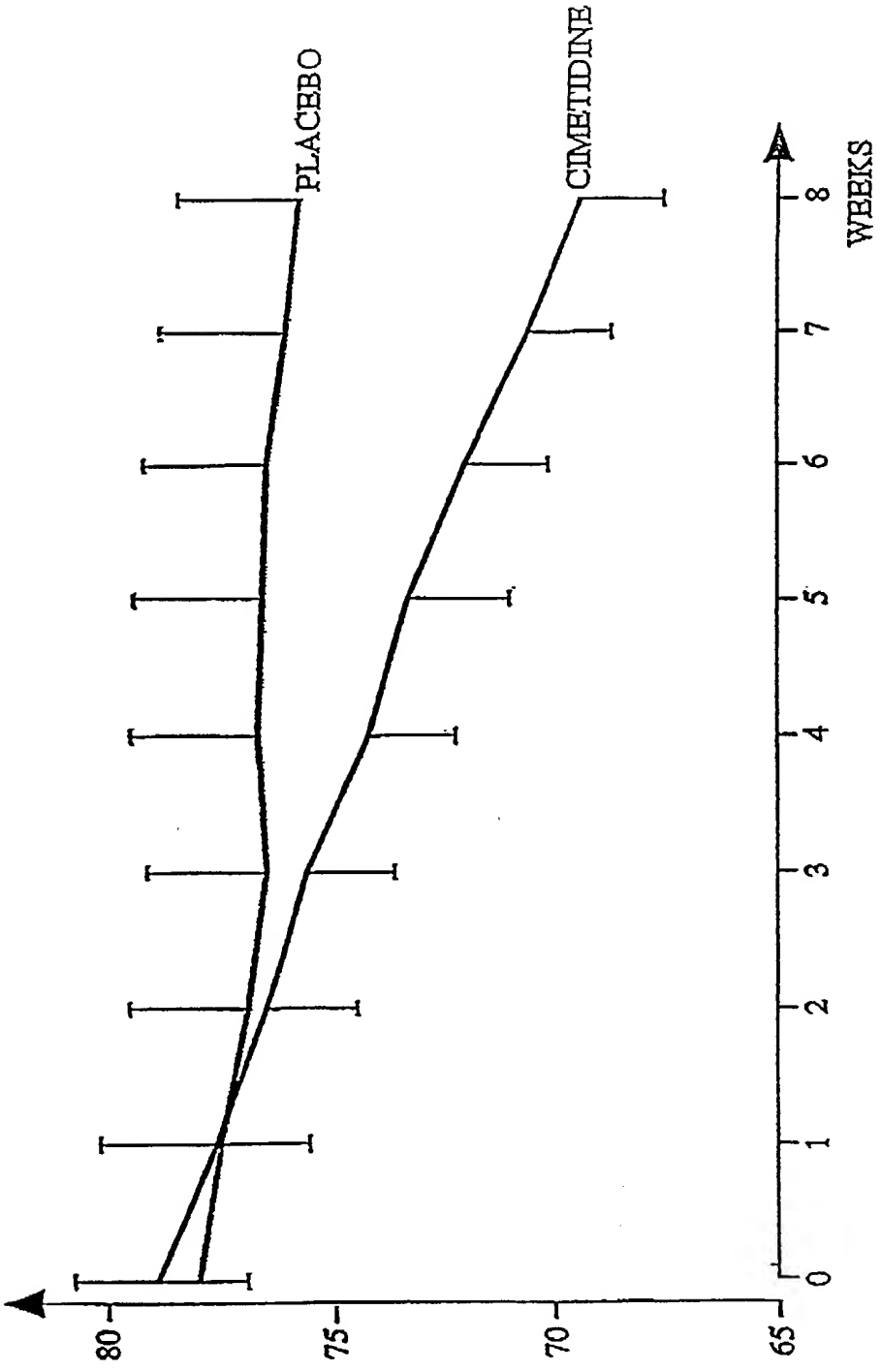

PLACEBO
CIMETIDINE
WEEKS
0
1
2
3
4
5
6
7
8
80
75
70
65
PATIENT WEIGHT (AVERAGE) KG.

Figure II

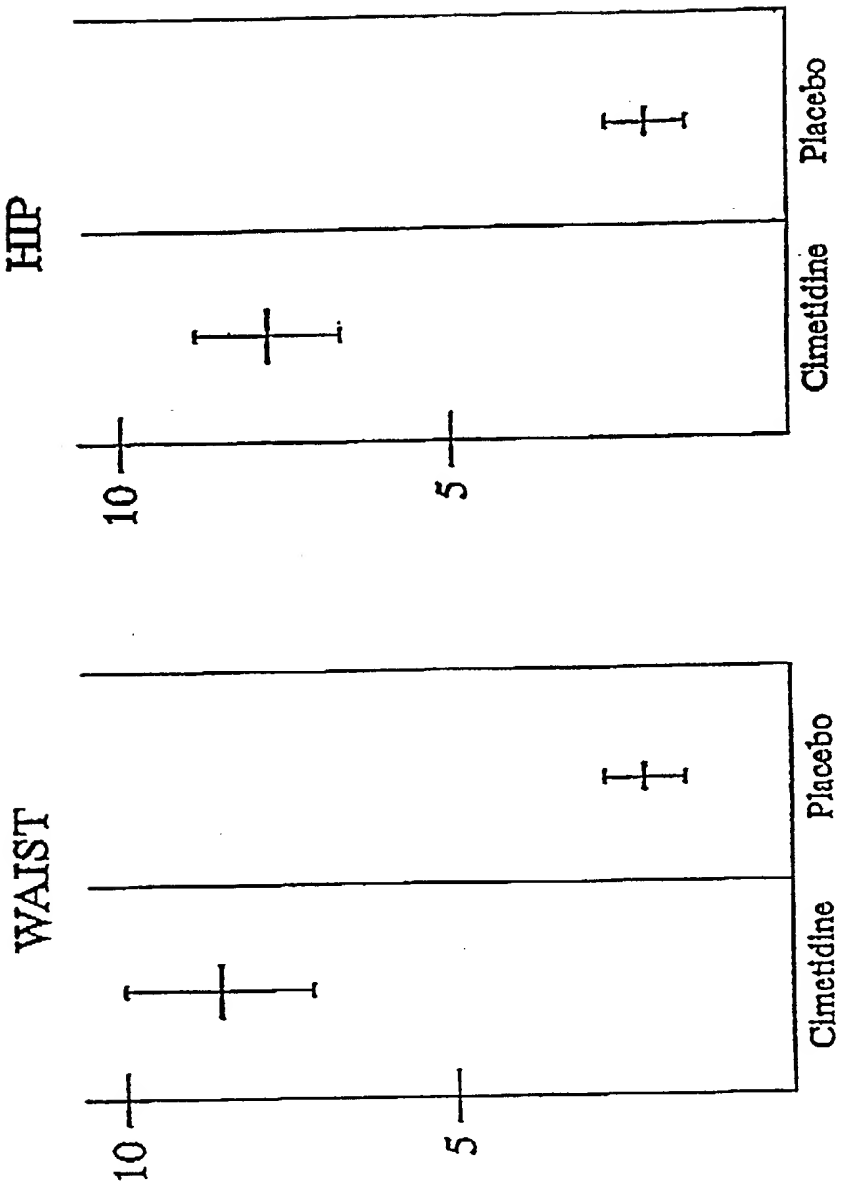
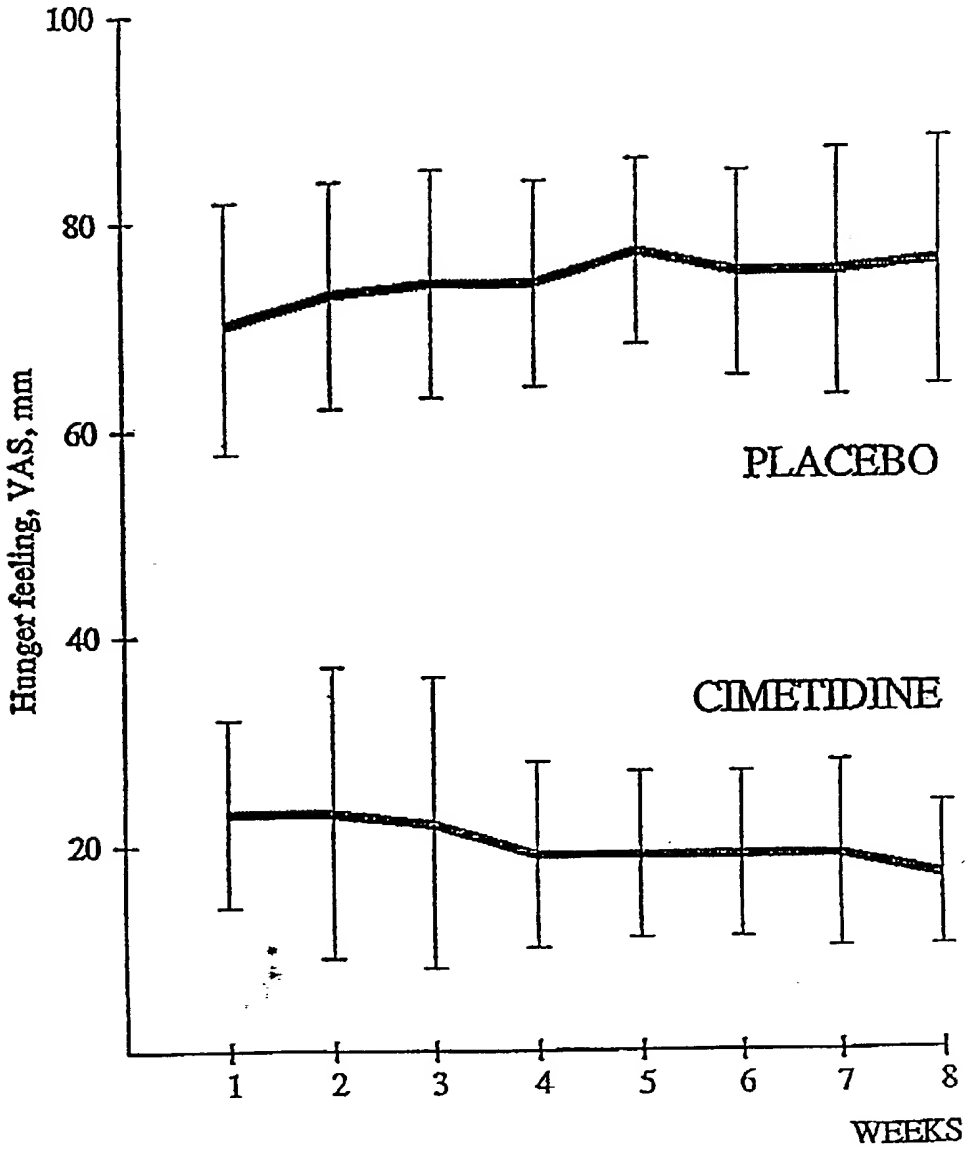

HIP
Placebo
Cimetidine
10
5
WAIST
Placebo
Cimetidine
10
5
Reduction, cm

Figure III


100
80
60
40
20
Hunger feeling, VAS, mm
PLACEBO
CIMETIDINE
1
2
3
4
5
6
7
8
WEEKS

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01120

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/415

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,4220653 (A.E. VIVINO) 2 September 1980, see the whole document, esp. claims (cited in the application)	1,2

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15-10-1991	09. 12. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Nuria TORIBIO

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. [X] Claim numbers 3-10 because they relate to subject matter not required to be searched by this Authority, namely:
see PCT-Rule 39.1(iv)

2. [ ] Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101120 SA 49438

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4220653	02-09-80	None	